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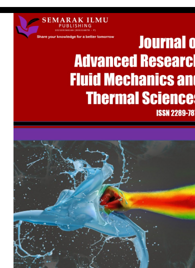

Correlation between extracellular cytokine gradients and intracellular calcium dynamics in neutrophils

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ABSTRACT

In the immune system, neutrophil movement toward the site of inflammation by concentration gradient is essential. In our previous studies, concentration gradient of cytokine on the neutrophil membrane is experimentally quantified. The results showed that the concentration gradient on the neutrophil membrane repeats positive and negative values while neutrophil moving. However, the key gap remains unclear: how external, membrane-scale cytokine gradient dynamics are coupled to intracellular signalling that drives protrusion and propulsion, and what the observed phase relationship implies for chemotaxis. In this study, the dynamics of intracellular calcium (Ca^{2+}) in neutrophils were measured, and these findings were compared with previously measured cytokine concentration gradients to verify their correlation. The results show three main findings: (1) Neither IL-8 stimulation nor neutrophil viability produced a statistically significant change in the global intracellular Ca^{2+}-indicator intensity or its decay rate. (2) The dominant frequencies of the membrane cytokine gradient and the intracellular Ca^{2+} gradient were similar, suggesting that external gradient dynamics and intracellular signaling are linked. (3) A consistent phase difference was observed between cytokine and Ca^{2+} gradients, indicating a delayed intracellular response to changes in membrane cytokine gradients. These findings support a mechanistic role of calcium signaling in neutrophil propulsion and provide quantitative constraints for chemotaxis models.

Keywords:

Neutrophil, Chemotaxis, Concentration gradient, Cytokine, Calcium ion

1. Introduction

Development of medical micro robotic devices have been focused over the past decades for targeted delivery, precision surgery, sensing and nanosurgery [1-4]. Despite great expectations, most of the past demonstrations are primarily in vitro conditions. Because there are several major issues including propulsion through complex media (such as blood, mucus, and vitreous) as well as deep tissue imaging and control in vivo [5-7]. Microscale swimmer's propulsion including spermatozoa and kind of bacteria are often considered as the power source of micro robotic devices. Particularly, neutrophil is highly biocompatible and unharmful in vivo. It has been reported that the efficiency of drug delivery to inflammatory regions has been significantly improved by utilizing neutrophils as drug carriers [8].

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Neutrophil is induced in the direction of high cytokine concentrations. The chemotaxis of neutrophils in the blood is an important component of the immune system in vivo, but the detailed driving mechanism is still unclear. In our previous studies, concentration gradient of cytokine on the surrounding fluid and neutrophil membrane is experimentally examined [9,10]. The results showed that the concentration gradient on the neutrophil membrane repeats positive and negative values while the concentration gradient in the surrounding fluid is constant. However, it remains unclear which intracellular signaling processes encode these external gradient dynamics and how they translate into protrusion generation and net propulsion, particularly the biological meaning of the observed frequency and phase relationships. This study addresses this gap by quantifying intracellular Ca^{2+} dynamics and directly comparing their frequency and phase to the membrane cytokine gradient.

This paper focuses on the internal dynamics of neutrophil to investigate the mechanism of neutrophil propulsion. It is known that cell propulsion forth is generated by internal calcium ion signalling [11-13]. Calcium ions play a critical role in cell signalling processes and function as messengers in many physiological responses, such as chemotaxis. The role of calcium ions in vivo is diverse, including activation of smooth muscle contraction and endothelial cell isolation. The increase in calcium ion concentrations is a rapid phenomenon associated with neutrophil activation. In addition, calcium ion dynamics are associated with cytoskeletal rearrangements and for generating the forces for cell move and deformation. Therefore, in order to understand the roll of cells, subcellular measurement of calcium ion is required. It is one of the most commonly used measuring method for quantifying receptor stimulation. Cytokines bind to seven trans-membrane, G-protein coupled cytokine receptors expressed on the surface of neutrophil initiating rapid intracellular signalling, including calcium mobilization, cytoskeletal rearrangements, and ultimately directed cell migration [14].

In this paper, calcium ion concentration gradient within neutrophils are measured and compared with external cytokine concentration gradient. First, to examine the effect of cytokines on calcium ions, calcium ion concentration in neutrophils is measured with and without cytokines. Second, to examine the effect of neutrophil death on calcium ion concentration, the calcium ion concentration on dead neutrophils is measured. Finally, to compare with the periodically changes of cytokine concentration gradient shown in previous sections, the calcium ion concentration gradient is measured. By this approach, the relationship between the calcium ion concentration gradient and half-rotation is investigated.

2. Neutrophil driving mechanism

It is generally known that some microscale particle moving in a liquid like neutrophil is driven by the Marangoni effect. Neutrophil is assumed as microparticle because their size range is from 6 μm to 8 μm. In this paper, to express neutrophil movement quantitively, the neutrophil propulsion mechanism is postulated by the Marangoni effect. The Marangoni effect is a passive motion caused by the non-uniformity of the interfacial tension working on particles in a liquid. One-dimensional neutrophil’s moving toward the x-axis is considered. The relationship between the force F working on the particle by the Marangoni effect and the cytokine concentration at a constant temperature is shown below [15].

$$F = \alpha \ (\mathrm{d}C/\mathrm{d}x) \tag{1}$$

where α is constant, C is concentration of cytokine and x is the position of neutrophil. Assuming that the particle is spherical and rigid, the particle Reynolds number ($Re = RV\rho/\eta$) is less than 1, and the dynamics in the solution layer itself is negligible where ρ is solution density and η is viscosity. The force F working on the particle is expressed by the velocity V from Stokes' resistance law as follows [16]:

$$F = 6\pi R\eta V \tag{2}$$

Since the force F in Eq. (1) and Eq. (2) are equal

$$\alpha\,(dC/dx) = 6\pi R\eta V \tag{3}$$

V is expressed using the proportionality constant k as follows:

$$V = k\,(dC/dx) \tag{4}$$

From this relationship, the neutrophil velocity is represented by the cytokine concentration gradient on the membrane. However, the relationship between the calcium ions dynamics inside neutrophils and the cytokines dynamics outside has not been elucidated. To address this issue, the concentration gradient of calcium ion is measured and compared with that of cytokine.

3. Methodology

3.1 Isolation of neutrophil

Neutrophils used in the observational experiments in this paper are isolated from the fresh porcine blood. Isolation methods have been referred to in the literature of Goldsmith et al. [18]. For precipitating red blood cells, the blood with heparin is left for about 60 minutes at 20℃. After this process, the supernatant containing neutrophil components is retrieved and centrifuged at 2000 rpm for 10 minutes at 4 °C using a cooling centrifuge (KUBOTA, personal cooling centrifuge 2700). To maintain their properties, percoll is used in centrifugation. To get sediments containing neutrophils, the supernatant rich in mononuclear cells is extracted after centrifugation. Finally, the suspension was centrifuged at 100 g for 8 min and the neutrophil pellet is resuspended in 0.3 ~ 0.5 ml of Tyrode's containing 0.25% human serum albumin (HSA). The solution was maintained at PH 7.4 to mimic in vivo conditions. A turbid suspension containing 15,000 to 25,000 neutrophils/μl is produced by this method. To adjust the temperature of the dispersion to 20 °C, the experiment is started 1 hour after isolation.

3.2 Fluorescent labeling of calcium ions

After isolation, calcium ions in the dispersion are antibody-labeled by the indicator. As calcium ion indicator, fura-2 AM is used. When calcium ion binding with fura-2, it emits the amplitude of the excitation spectrum at 340 nm at the expense of that at 380 nm, with little change in the peak emission spectrum between 505 ~ 520 nm. Based on the properties, a ratiometric measurement of intracellular calcium ion concentration can be obtained through the 340/380 nm ratio by calibrating the system with maximal and minimal ratio values, and the calcium ion dissociation constant (Kd) of fura-2 (near 224 nM in physiological intracellular medium). Such ratioing largely cancels out the effects of cell thickness, dye content or instrumental efficiency allowing more accurate

measurements of calcium ion [18-20]. In this study, to determine the concentration of calcium ions inside neutrophils during cytokine working, only the luminescence intensity by fura-2 AM is measured instead of ratiometric measurements. Then, to investigate the correlation between cytokine concentration gradient and calcium ion concentration gradient, the exact calcium ion concentration inside neutrophils is measured by ratiometric measurement.

Fura-2 AM is dissolved in Dimethyl sulfoxide (DMSO). DMSO is a nonprotic polar solvent that dissolves many organic and inorganic compounds well and is a safe solvent. 10 μL of fura-2 AM solution is dropped into the neutrophil dispersion, and the solution is incubated in a cool, dark place for 1 hour to allow the calcium ions in the neutrophils to bind to the fura-2 AM. The neutrophils emit calcium ions by irradiating them with excitation light from a fura-2 AM calcium imaging-compatible light source (pE340, Givetechs), and the intensity of the emission is captured as the calcium ion concentration. The effect of fluorescent labeling by fura-2 decreases with time. To investigate the effect of cytokine on calcium ion concentration, the speed of decrease in luminescence intensity is also calculated.

3.3 Observation method

After fluorescence labeling, the neutrophil dispersion is transferred onto a cover glass. As shown in Fig. 1, 10 ng/ml of cytokine solution is inserted into the dispersion containing neutrophils to form concentration gradient with pipette. The diffusion of cytokine and the neutrophil's move are photographed with a CCD camera (Watec, WAT-910HX). Fig. 2 (a) and Fig. 2 (b) show the images of neutrophil. Fig. 2 (c) and Fig. 2 (d) show their luminance intensity distributions at 30-second intervals.

As a chemotactic factor, cytokine IL-8 is used, which is produced by monocytes and lymphocytes. It acts on leukocyte cells such as neutrophils. Cytokine solution is inserted from the left side of the image. The time neutrophils begin to move is defined as t = 0 s. This figure also shows that the neutrophil moves in the direction of cytokine insertion. The neutrophil velocity is calculated from the distance moved in 70 seconds. However, movement in the y direction is ignored and only the x direction is measured. Focusing on the changes in calcium ion concentration during cytokine working, calcium ion concentration and its gradient are calculated. To measure the concentration gradient, the luminescence intensity is captured as the calcium ion concentration. Averaging the y-axis range of the luminance intensity where neutrophils exist, the one-dimensional concentration distribution

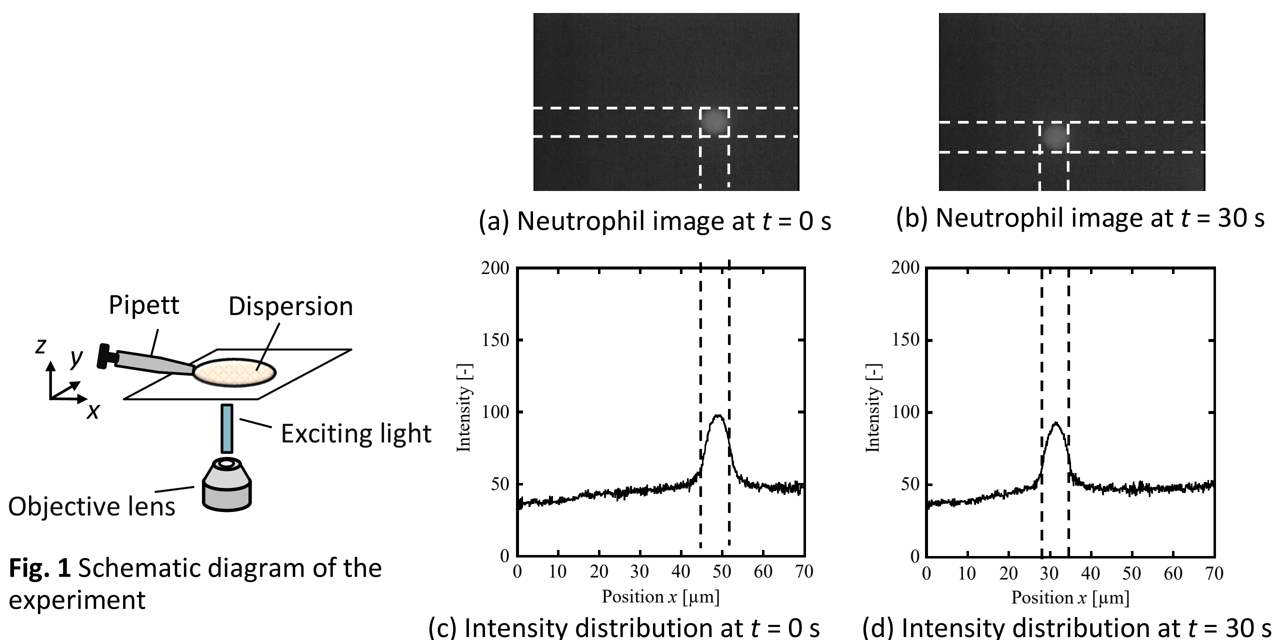


Fig. 1 Schematic diagram of the experiment

(a) Neutrophil image at t = 0 s
(b) Neutrophil image at t = 30 s
(c) Intensity distribution at t = 0 s
(d) Intensity distribution at t = 30 s

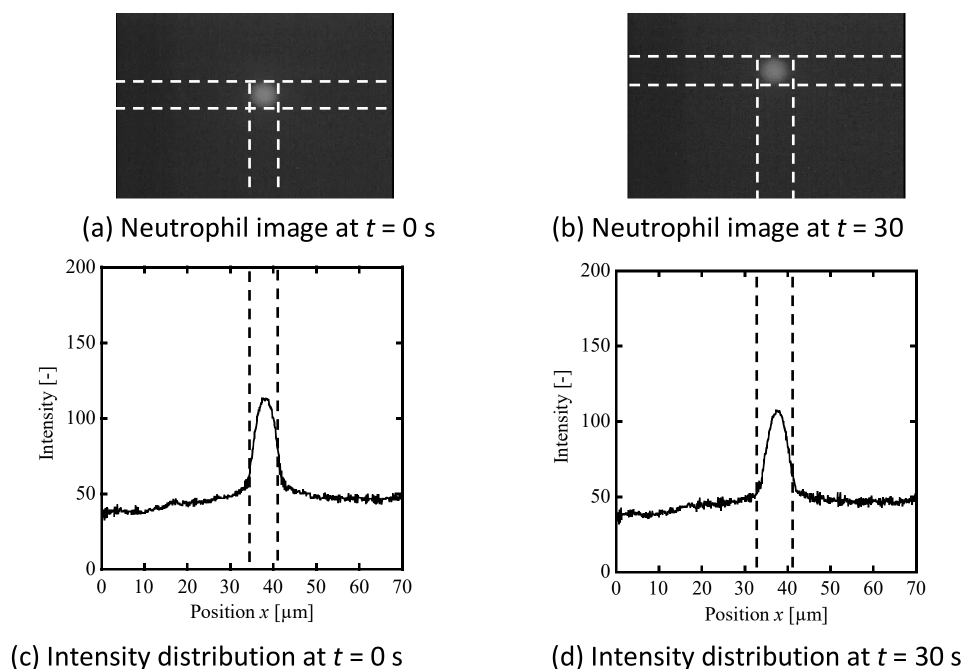
Fig. 2 Neutrophil images and intensity distributions with cytokine

is obtained. The minimum video resolution is 0.1 µm. The calcium ion concentration gradient on the neutrophil membrane is obtained by linear approximation of 10 points (2 µm) before and after the neutrophil center coordinates. To obtain the frequency of the time history of the concentration gradient on the neutrophil membrane, FFT (Fast Fourier Transform) analysis is also applied. In the experimental system used in this study, it is not possible to simultaneously measure calcium ion concentrations inside neutrophils and cytokine concentrations outside. When comparing cytokines and calcium ion concentration gradients, each measured from a different individual is used.

4. Results

4.1 Comparison of calcium ion concentrations with and without cytokine

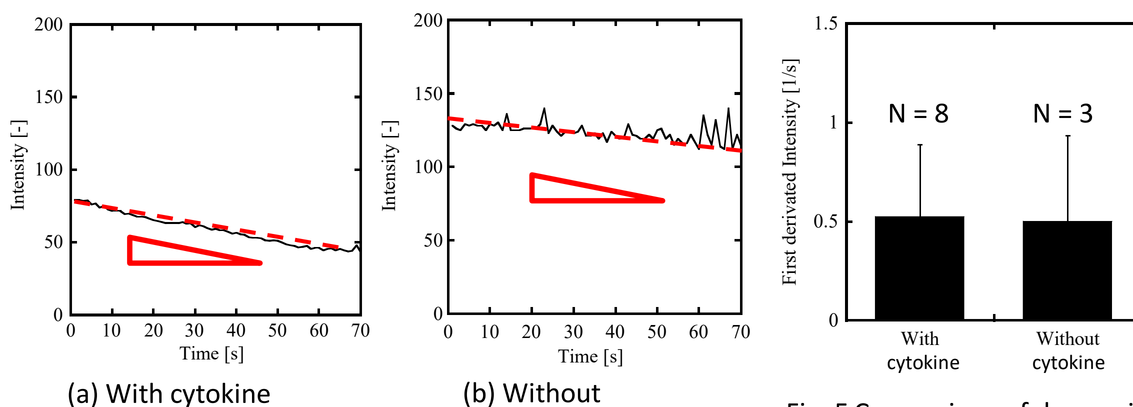
Fig. 3 (a) and Fig. 3 (b) show the images of neutrophil at 30-second intervals without cytokine. Fig. 3 (c) and Fig. 3 (d) show their luminance intensity distributions at 30-second intervals without cytokine. In the case of without cytokine, neutrophil hardly move in the x direction compared to the case of with cytokine shown in Fig. 2. Therefore, the movement in the y direction is considered to be



(a) Neutrophil image at t = 0 s (b) Neutrophil image at t = 30

(c) Intensity distribution at t = 0 s (d) Intensity distribution at t = 30 s

Fig. 3. Neutrophil images and intensity distributions without cytokine



(a) With cytokine (b) Without

Fig. 4. Time history of luminance intensity

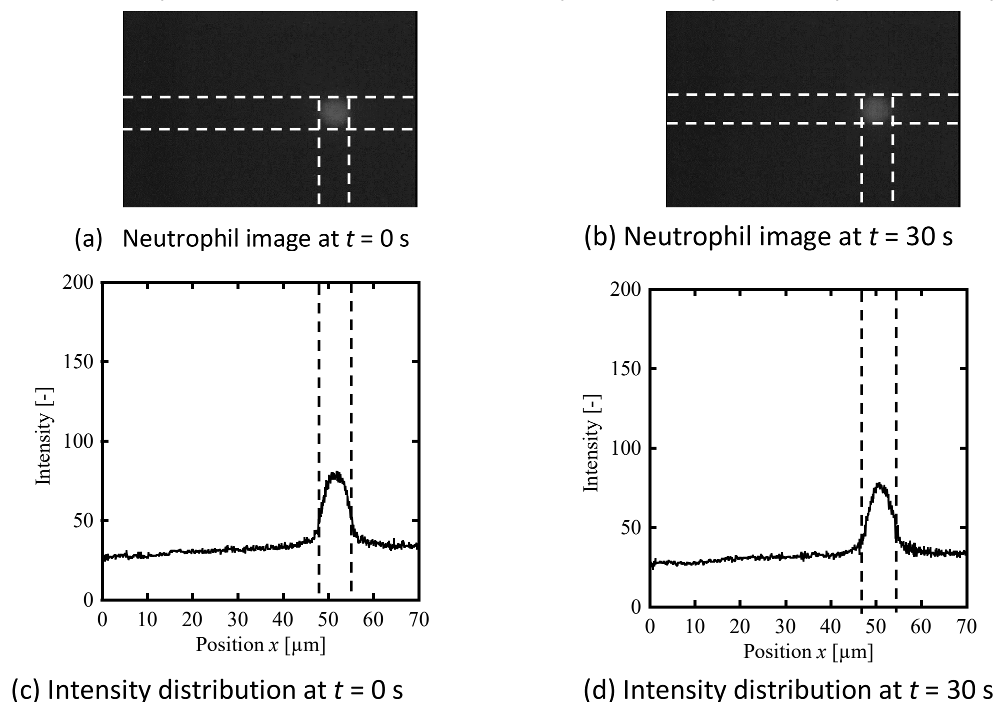
Fig. 5 Comparison of decreasing speed in luminance intensity

due to convection during insertion. However, calcium ion in neutrophil emit light as in the case of with cytokine. In general, calcium ion signaling in neutrophil is known to be triggered by cytokine. This result indicates that the total amount of calcium ions inside neutrophils is not consumed by signaling. The luminescence intensity of calcium ions is higher at the center of the neutrophil and lower at the position far from the neutrophil. The distribution of surrounding fluid also does not change significantly with or without cytokine. Therefore, it is found that the existence of cytokine does not affect the calcium ion concentration not only on the neutrophils but also in the surrounding fluid.

Fig. 4 (a) and Fig. 4 (b) show the time history of luminance intensity on neutrophil with and without cytokine. This result indicates that calcium ion concentrations decrease with and without cytokine. These graphs are used to calculate the decreasing speed in luminance intensity. The decreasing speed is calculated by the time derivative of the intensity. In both cases, the calcium ion concentration inside neutrophils decreases linearly. Fig. 5 shows the decreasing speed in luminance intensity. Error bars represent a 95% confidence interval. The speed is almost the same with and without cytokine. The intensity of calcium ion staining by fura-2 decreases with time. From these results, the binding of calcium ion with fura-2 in this experimental condition is not affected by cytokine. Neutrophils in the case of with cytokine are triggered to move, but no associated increase or decrease in calcium ions has been observed.

4.2 Comparison of calcium ion concentrations by neutrophil living and dead

To investigate the effect of neutrophil living and dead on the calcium ion concentrations, the calcium ion concentrations on the neutrophils that have lost their function after 10 hours of blood collection (the life span of the neutrophils) are measured. At this time, dead neutrophil is under cytokine concentration gradient. Fig. 6 (a) and Fig. 6 (b) show the images at 30-second intervals of dead neutrophil. Fig. 6 (c) and Fig. 6 (d) show their luminance intensity distributions at 30-second intervals of dead neutrophil. In the case of dead neutrophil, neutrophil hardly move compared to the



(a) Neutrophil image at t = 0 s
(b) Neutrophil image at t = 30 s
(c) Intensity distribution at t = 0 s
(d) Intensity distribution at t = 30 s

Fig. 6 Dead neutrophil images and intensity distributions with cytokine

case of living neutrophil. However, calcium ion in neutrophil emit light as in the case of living neutrophil. Neutrophil living or dead as well as the with or without cytokine does not affect the binding or distribution of calcium ions and fura-2.

Fig. 7 (a) and Fig. 7 (b) show the time history of luminance intensity in living and dead neutrophil. This result indicates that calcium ion concentrations decrease regardless of whether neutrophils are living or dead. These graphs are used to calculate the decreasing speed in luminance intensity. In both cases, the calcium ion concentration inside neutrophils decreases linearly.

Fig. 8 shows the decreasing speed in luminance intensity. The speed is almost same in living and dead neutrophil. Therefore, the binding of calcium ion with fura-2 is not affected by neutrophil's living or dead as well as with and without cytokine. These tendencies are almost similar to those with and without cytokine.

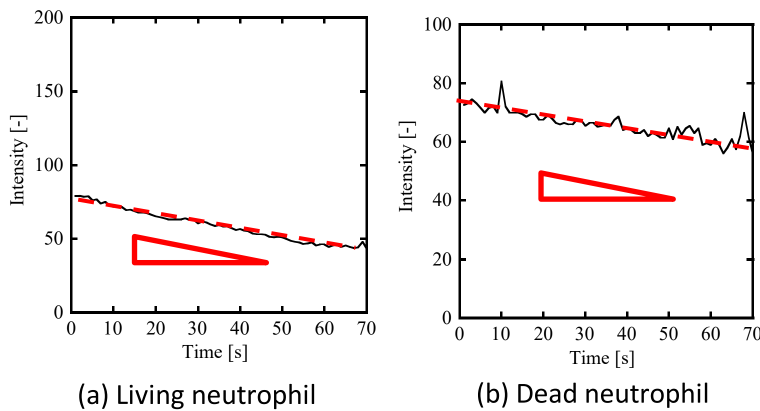


Fig. 7 Time history of luminance intensity for living and dead neutrophil

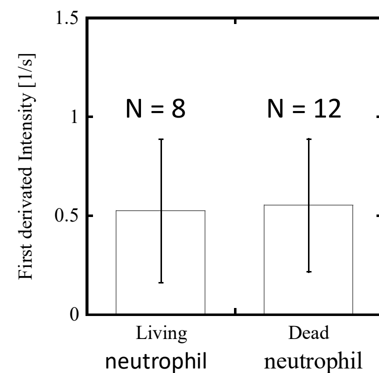


Fig. 8 Comparison of decreasing speed in luminance intensity in living and dead neutrophil

4.3 Comparison of calcium ion concentrations gradient and cytokine concentration gradients

The purpose of this section is to measure the dynamics of calcium concentration distribution inside neutrophil and to elucidate the relationship with periodically changes in the cytokine concentration gradient on the membrane. However, the fluorescence wavelength of FITC (480 ~ 490 nm), which fluorescently labels cytokines, is close as that of calcium ions (340 nm), making simultaneous measurement of cytokines and calcium ions impossible in current experimental systems. Therefore, the two measurement experiments for cytokines and calcium ion are done separately. Cytokine and calcium ion concentration gradients are obtained and compared with respect to the time at which neutrophils begin to move. The time at which neutrophils begin to move is defined as t = 0 s. The results of cytokine and calcium ion measurements from t = 0 s are overlaid on each other and correlations are examined. Fig. 9 shows the contour of luminance intensity every 25 s. The images are enlarged to show the distribution on the neutrophil. In the case of cytokine shown in Fig. 9(a), at t = 25 s, cytokine concentration is higher on the left side of neutrophils, but at t = 75 s, it is higher on the right side. It indicates that the cytokine concentration on neutrophil membrane changes with time. In the case of calcium ion shown in Fig. 9(b), the concentration bias is more clearly shown than the case of cytokine. However, changes in concentration with time are not very large. In order to determine the correlation between the changes in the two concentrations, the gradients of those are calculated for each cases.

Fig. 10 shows the time history of cytokine and calcium ion concentration gradient. Cytokine is shown as black line and calcium ion as red line. It is found that the calcium ion concentration gradient

is not constant but changes periodically like cytokine concentration gradient. There are two possible reasons for this. The first one is calcium ion signaling was caused by the action of cytokine concentration gradient. The second one is that neutrophil's half rotation caused a non-uniform distribution of calcium ion concentrations. Furthermore, there is a phase difference between the two waveforms. One possible reason for this is that calcium ion transport occurs several tens of seconds after cytokines reach the membrane. This phase lag may reflect the time required for receptor activation, downstream signaling, and redistribution of intracellular Ca^{2+} that precedes protrusion remodeling.

Next, in order to investigate the frequency, FFT analysis is done to the time histories of the cytokine and calcium ion concentration gradients. Fig. 11 shows the frequency of cytokine and calcium ion concentration gradients. It is found that frequency is almost the same for cytokine and calcium ion. It indicates that the frequency of cytokine and calcium ion concentration gradient are closely related. The possibility of half-rotation has been derived from the fact that the cytokine concentration gradient on the membrane changes periodically. In the future, it is necessary to design

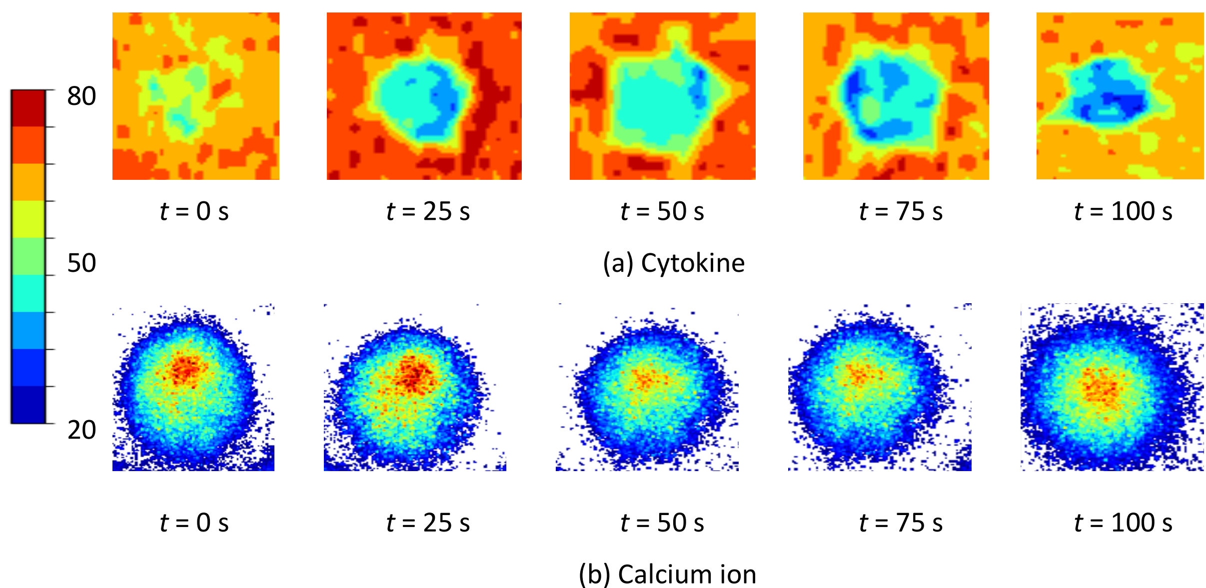


Fig. 9 The contour of luminance intensity every

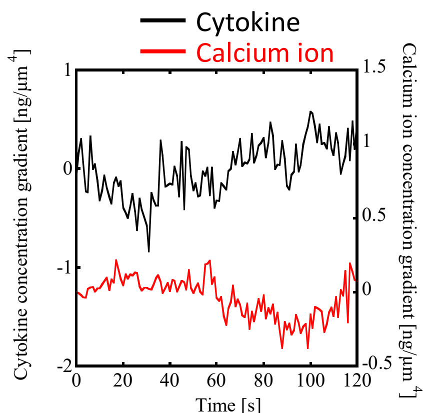


Fig. 10 Time history of cytokine and calcium ion concentration gradient

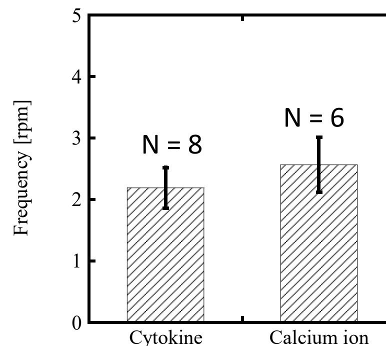


Fig. 11 Comparison of frequencies of cytokine and calcium ion concentration gradients

an experimental system that simultaneously measures calcium ions and cytokines and to consider the relationship between cytokines and calcium ions in more detail.

5. Discussion

In this study, calcium ion concentrations within neutrophils have been measured and compared with external cytokine concentrations. It was shown that a correlation between the cytokine concentration gradient on the membrane and the internal calcium ion concentration gradient was shown. The pathways involving calcium signaling are numerous and are known to be essential regulators of all stages of the chemotaxis cycle [21, 22]. Most studies are concerned with specific functional activities and describe observations for quite short periods of time, such as during the initial expression of calcium transients or during each move response. Many of these studies have investigated signaling pathways by microscopically observing the bias in calcium ion concentrations inside neutrophils. One reason why macroscopic concentration changes have not been investigated like this study is that multiple changes happen in parallel within the neutrophil.

The case of with or without cytokine did not affect the calcium ion concentration inside neutrophils under the conditions of the present experiment. The reason for this is thought to be that the type of cytokine used was IL-8. Inflammatory cytokines such as TNF-alpha and IL-13 were shown to increase the agonist-induced calcium ion response in ASM [23]. These myocytes allow for muscle contraction by regulating the uptake, storage, and release of calcium ions. Neutrophils don't have such functions, and the type of cytokine is different. The type of cytokine used in this study is IL-8, which is specifically associated with just move. The results also showed a tendency for the luminescence intensity at the center of neutrophils to be higher under all conditions. Calcium ion bias within neutrophils was not quantified. Therefore, a better resolution camera is needed to detect the dynamics of calcium ions inside neutrophils during the action of cytokine.

The case of living or dead did not also affect the calcium ion concentration inside neutrophils under the conditions of the present experiment. Neutrophils that had reached the end of their life span and dead were observed in this study. In addition to passive death such as life span, there is another type of active death called apoptosis. Apoptosis removes the risk of neutrophils taking in nutrients unnecessarily from the outside. In this type of death, the calcium ion concentration inside neutrophils can be changed. It is known that when neutrophils die actively by apoptosis, the influx of calcium ions is gradually reduced. Neutrophils in this study did not exchange calcium ions with the outside. However, it is possible that some of the living neutrophils were in the process of apoptosis. In other words, the change in calcium ion concentration inside the original neutrophil may be greater than in the experiment.

In this study, neutrophil motion was observed in a pathogen-free environment. The experimental and in vivo environments differ in this respect. Therefore, there was no need for external calcium ion concentrations or calcium ion exchange in experimental environment of this study. In vivo, calcium ion concentrations change more actively inside neutrophils during the action of cytokine. Hoth's group showed that mitochondria play an important role in store operated calcium ion (SOC) opening in T lymphocytes and Gilabert's group in basophilic leukaemia, a myeloid cell line [24, 25]. Mitochondria are known to take up calcium ions from the cytosol and are located near the endoplasmic reticulum. They were thought to help empty calcium ion from storage or lowering local cytosolic calcium ion below levels that could activate SOC. This indicates that the total calcium ion concentration inside neutrophils changes depending on the presence or absence of specific cells such as mitochondria. The results of environment in this study can be changeable in environments with mitochondria. In the future, experiments in an environment with mitochondria will be necessary.

6. Conclusions

In this study, the coupling between extracellular cytokine gradient dynamics and intracellular Ca^{2+} dynamics in neutrophils was investigated experimentally. The main findings are summarized as follows.

I. Cytokine and neutrophil viability don't affect the calcium ion concentration inside neutrophil.
II. The frequencies of cytokine and calcium ion dynamics are almost the same value.
III. There is a phase difference in the dynamics of cytokine and calcium ion.

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